Reciprocal Interaction of 24-Hour Blood Pressure Variability and Systolic Blood Pressure on Outcome in Stroke Thrombolysis

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Background and Purpose—Significance and management of blood pressure (BP) changes in acute stroke care are unclear. Here, we aimed to investigate the impact of 24-hour BP variability (BPV) on outcome in patients with acute ischemic stroke treated with intravenous thrombolysis.

Methods—From the Safe Implementation of Treatment in Stroke International Stroke Thrombolysis registry, 28 976 patients with documented pre-treatment systolic BP at 2 and 24 hours were analyzed. The primary measure of BP variability was successive variability. Data were preprocessed using coarsened exact matching. We assessed early neurological improvement, symptomatic intracerebral hemorrhage (SICH), and long-term functional outcome (modified Rankin Scale [mRS] at 90 days) by binary and ordinal regression analyses.

Results—Attempts to explain successive variation for analysis of BPV with patients characteristics at admission found systolic BP (5.5% variance) to be most influential, yet 92% of BPV variance remained unexplained. Independently from systolic BP, successive variation for analysis of BPV was associated with poor functional outcome mRS score of 0 to 2 (odds ratio [OR], 0.94; 95% confidence interval [CI], 0.90–0.98), disadvantage across the shift of mRS (OR, 1.04; 95% CI, 1.01–1.08), mortality (OR, 1.10; 95% CI, 1.01–1.08), $SICH_{SITS}$ (OR, 1.14; 95% CI, 1.06–1.23), and $SICH_{ECASS}$ (OR, 1.24; 95% CI, 1.10–1.40; ECASS [European Cooperative Acute Stroke Study 2]). Analyzing successive variation for analysis of BPV as a function of pre-treatment, systolic BP significantly improved the prediction of functional outcome (mRS score of 0–1, mRS score of 0–2, neurological improvement, mRS-shift: all $P_{interaction}<0.01$). Excluding patients with atrial fibrillation in a sensitivity analysis gave consistent results overall.

Conclusions—This study suggests the need for a more individual BP management accounting for pre-treatment BP and the acute BP course (ie, BPV) to achieve best possible outcome for the patient. **(*Stroke*. 2017;48:1827-1834. DOI: 10.1161/STROKEAHA.117.016876.)**

Key Words: atrial fibrillation ■ blood pressure ■ blood pressure variability ■ cerebral hemorrhage ■ regression analysis ■ stroke ■ thrombolysis

In the acute phase of stroke, up to three quarters of patients experience high blood pressure (BP), a phenomenon yet understood incompletely.[1,2] Guidelines recommend tolerating a BP up to 220/120 mm Hg, 185/110 mm Hg, and 180/105 mm Hg in patients in general, before, and after administering intravenous thrombolysis (IVT) because of the most feared complication symptomatic intracerebral hemorrhage (SICH).[3] Most observational studies found an association between higher admission systolic BP (BP_{sys}) and worse outcome describing a distinct U-shaped admission BP_{sys} relation. Thereby, a range of 141 to 150 mmHg BP_{sys} yielded best functional outcome at 90 days after stroke.[4–8]

Even so, clinical trials investigating active BP lowering in acute ischemic stroke have not shown an advantage from BP intervention neither for safety nor for functional outcome.[9–12] One recent post hoc analysis from a clinical trial showed a

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positive association of BP lowering and functional outcome irrespective of whether the patient received IVT or not.[13] About bleeding complications after IVT, reports are conflicting where some reported an association between post-thrombolysis BP elevation and hemorrhagic transformation, but others did not.[14–16] The randomized ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study, BP arm) investigating superior efficacy and lower risk of any intracerebral hemorrhage of early intensive lowering of BP (systolic target 130–140 mm Hg) versus BP control as recommended in guidelines (systolic target <180 mm Hg) is ongoing, and results are anticipated in 2018.[17]

For several years, stroke neurologists have focused on not only standard BP parameters but also BP variability (BPV, for review Manning et al[18]). For the short-term BPV, higher BPV was shown to increase the rates of SICH, death, and poor outcome after stroke.[19–21] Recently, a post hoc analysis of 2 clinical trials investigating BPV (assessed as SD) showed no significant association with 2-week functional dependency after stroke and in-hospital mortality.[22] More recently, higher BPV within 24 hours after stroke was demonstrated to be associated with poor prognosis after IVT.[13,23]

BP management in acute ischemic stroke is relevant for clinical practice, but individual strategies are not yet established. Here, we determined the influence of BP and BPV during the first 24 hours on short- and long-term outcomes in a large international cohort of patients who received IVT, reflecting the status quo of BP management.

Methods

Study Setting

Acute ischemic stroke patients treated with IVT (Actilyse; Boehringer Ingelheim, Germany) and recorded in the Safe Implementation of Treatment in Stroke (SITS) international registry between 2002 and 2013 (https://sitsinternational.org) were considered for analysis (n=58 294). Only patients with complete baseline, imaging, outcome, and BP measurements (n=28.976; 49.7%) comprised the current study sample.[24]

The SITS registry is an ongoing large international registry prospectively enrolling at 1422 centers in 70 countries. Stroke centers contributing to SITS assessed stroke severity with the National Institutes of Health Stroke Scale (NIHSS) score. For full details of methodology including issues of management about patients data including source data and identification, the reader is kindly referred to previously published work.[24]

Definition of BPV

BP values in SITS were documented at least at 3 time points—pre-treatment, at 2 hours, and at 24 hours after IVT. At each time point, there was only 1 BP reading documented. Of these 3 systolic BP values, BPV was calculated. As primary measure of variability, we choose successive variation (SV) for analysis of BPV (BPV_{SV}) because it addresses the time sequence in measurements more appropriately than other measures.[25] SV was calculated as square root of average squared difference between 2 successive BP measurements according to following equation:

$$SV=\sqrt{\frac{1}{n-1}\sum_{i=1}^{n-1}\left(X_{i+1}-X_i\right)^2}$$

Outcome Definitions

Functional outcome at 3 months was measured by the modified Rankin Scale (mRS)—it ranges from 0 to 6. If raters judged 0 or 1, excellent functional outcome, and if 0 to 2, good or functional independent outcome was concluded.

The primary aim of this study was to investigate the relationship of the influence of BPV_{SV} and pre-treatment BP_{sys} on excellent and good outcomes after 3 months. In addition, an ordinal analysis of the 3-month mRS was performed. Recanalization leads to an improvement in early neurological outcome and may likely be associated with a drop in BP.[26–28] Because the overall number with documented cases of recanalization was low (<20%) and this was not the primary aim of the study, we chose 2 outcome definitions of early neurological improvement (ENI) within 24 hours as a proxy for presumed vessel patency: (1) $ENI_{20\%}$ defined as an improvement of ≥20% on the NIHSS because this definition was previously demonstrated to be the best predictor of functional 3-month outcome and (2) ENI_8 defined as an improvement of ≥8 points on the NIHSS.[29–31]

Safety measures included the occurrence of SICH after IVT according to SITS and ECASS-2 definitions (ECASS-2 [European Cooperative Acute Stroke Study 2]; in the online-only Data Supplement).

Ethics

Patients within SITS received thrombolysis as standard of care. This was a retrospective analysis. Therefore, new ethics review was not necessary for data analysis because ethical approvals had been obtained in countries where they are required. In other countries, SITS was approved as an anonymized register without need for ethical approval.

Statistical Analysis

For information how the sample was preprocessed—that is, imputation strategies, listwise deletion, and coarsened exact matching—we kindly refer the reader to the Methods in the online-only Data Supplement.

Normally distributed data are presented as mean and SD, non-normally distributed data as median and interquartile range. For categorical variables, counts and percentages are given. Univariate statistics used Student *t* test, Mann–Whitney *U* test, or χ^2 where appropriate.

Analysis of BPV

BPV_{SV} was primarily used as a continuous variable in all analyses. Importantly, BPV_{SV} was categorized for presentation purposes of the matched cohort only, representing cohorts of low (BPV_{SV} <15), medium (BPV_{SV} 15–29.9), high (BPV_{SV} 30–45), and highest (BPV_{SV} >45). Associations of covariates and factors on BPV_{SV} were tested by Spearman rank, a linear multivariable regression analysis further estimated the relevance of each variable in the presence of others. Association between BPV_{SV} and 3-month outcome was estimated by binomial and ordinal logistic regression. In multivariable regression analysis, adjustments were made for age, sex, NIHSS, BP_{sys}, history of arterial hypertension, history of diabetes mellitus, history of hypercholesterolemia, current smoking, previous stroke, history of atrial fibrillation (AF), and history of coronary heart failure.

We allowed for interactions of BP_{sys} and BPV_{SV} on a multiplicative scale and compared the model including the interaction with the main model by a likelihood ratio test.[32] For main predictors, a 2-sided $P<0.01$ and for interactions terms, a $P<0.05$ was considered as statistically significant. For odds ratios and 95% confidence intervals to reflect meaningful values (because of the high number of patients), reported odds ratios for continuous variables BPV_{SV} and BP_{sys} reflect a change from the 25th to the 75th percentile. Graphical presentation of the interaction, $BP_{sys}\times BPV_{SV}$, is on the scale of predicted probabilities using example values of BPV_{SV} (0, 15, 30, 45, and 60) varying across all values of BP_{sys}.

Statistical analysis was performed with Statistical Package for the Social Sciences, SPSS (Released 2012; IBM SPSS Statistics for Windows, version 21.0; IBM Corp, Armonk, NY) and R (R Core Team 2014. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/).

Sensitivity Analysis

Patients who had AF usually present with higher variability in BP readings.[33] Therefore, we excluded patients who had known history of AF at presentation, testing only non-AF patients for sensitivity analysis. This sensitivity analysis should therefore exclude the contribution of the AF population to BPV although we had no information on newly diagnosed AF in this data set.

Results

Patients Characteristics According to BPV_{SV}

Of 28 976 patients in the entire cohort, 16 434 patients remained after preprocessing. Table 1 shows patients baseline characteristics in the entire cohort and the matched cohort. BPV_{SV} was categorized into groups (<15, 15–29.9, 30–45, and >45) for presentation purposes only reflecting 60.2%, 32.4%, 6.0%, and 1.4% of the matched cohort, respectively.

Successive BPV

Associations between BPV_{SV} and other covariates were found. Best associative strength was found in a positive, moderate correlation of pre-treatment systolic BP (r=0.267; P<0.000001) and BPV_{SV}. Furthermore, longer stroke onset to treatment times (r=0.029; P=0.000001) and higher age (r=0.101; P<0.000001) were weakly correlated to higher BPV_{SV}, whereas correlation between BPV_{SV} and NIHSS (r=–0.013; P=0.024) was hardly evident. Patients experiencing higher BPV_{SV} were women and had history of hypertension, diabetes mellitus, hypercholesterolemia, AF, smoking, and prior stroke (all P<0.01). No association was found for patients with history of heart failure (P=0.787).

To further determine which baseline factor would explain most of the variance of BPV_{SV}, linear multivariable regression analysis demonstrated pre-treatment systolic BP to be most

Table 1. Patients Characteristics and Univariate Outcome in the Entire Cohort, Matched Cohort Including Successive Blood Pressure Variability

	Entire Cohort	Matched Cohort	Successive Blood Pressure Variability Categories			
	All (n=28 976)	All (n=16 434)	<15 (n=9893)	15–29.9 (n=5322)	30–45 (n=988)	>45 (n=231)
Patients characteristics						
Age, y, median (IQR, 25–75)	70 (60–77)	71 (63–77)	71 (63–77)	71 (63–77)	73 (65–77)	73 (66–78)
Baseline NIHSS, median (IQR, 25–75)	11 (7–17)	11 (7–16)	11 (7–16)	11 (7–16)	12 (7–17)	12 (7–16)
Onset to treatment time, min	147 (119–175)	145 (120–170)	145 (120–170)	146 (120–170)	145 (120–170)	150 (120–174)
Pre-treatment systolic blood pressure	150 (136–167)	155 (140–168)	155 (140–168)	156 (141–169)	157 (141–170)	160 (140–173)
Sex, female, n (%)	12373 (42.7)	6625 (40.3)	3950 (39.9)	2150 (40.4)	427 (43.2)	98 (42.4)
History of arterial hypertension, n (%)	18309 (63.2)	11455 (69.7)	6880 (69.5)	3651 (68.6)	738 (74.7)	186 (80.5)
History of diabetes mellitus, n (%)	4899 (16.9)	1809 (11)	1080 (10.9)	566 (10.6)	128 (13)	35 (15.2)
History of hypercholesterolemia, n (%)	9825 (33.9)	5706 (34.7)	3356 (33.9)	1919 (36.1)	362 (36.6)	69 (29.9)
History of active smoking, n (%)	6197 (21.4)	3364 (20.5)	1998 (20.2)	1135 (21.3)	184 (18.6)	47 (20.3)
Prior stroke, n (%)	3617 (12.5)	2157 (13.1)	1287 (13)	655 (12.3)	178 (18)	37 (16)
History of atrial fibrillation, n (%)	6641 (22.9)	3975 (24.2)	2338 (23.6)	1316 (24.7)	247 (25)	74 (32)
History of coronary heart failure, n (%)	2422 (8.4)	1304 (7.9)	747 (7.6)	444 (8.3)	89 (9)	24 (10.4)
Outcome definitions						
Symptomatic Intracerebral hemorrhage						
SITS definition, n (%)	412 (1.4)	272 (1.7)	144 (1.5)	96 (1.8)	23 (2.3)	9 (3.9)
ECASS-2 definition, n (%)	1322 (4.6)	755 (4.6)	426 (4.3)	244 (4.6)	64 (6.5)	21 (9.1)
Modified Rankin Scale at 90 d, n (%)						
0	6602 (22.8)	3732 (22.7)	2264 (22.9)	1209 (22.7)	214 (21.7)	45 (19.5)
1	6088 (21)	3570 (21.7)	2151 (21.7)	1200 (22.5)	181 (18.3)	38 (16.5)
2	4567 (15.8)	2660 (16.2)	1631 (16.5)	853 (16)	146 (14.8)	30 (13)
3	3729 (12.9)	2106 (12.8)	1264 (12.8)	682 (12.8)	124 (12.6)	36 (15.6)
4	3239 (11.2)	1879 (11.4)	1131 (11.4)	589 (11.1)	123 (12.4)	36 (15.6)
5	1418 (4.9)	763 (4.6)	439 (4.4)	252 (4.7)	59 (6)	13 (5.6)
6	3333 (11.5)	1724 (10.5)	1013 (10.2)	537 (10.1)	141 (14.3)	33 (14.3)
Early neurological improvement <24 h						
8 points less on NIHSS	6411 (22.1)	3533 (21.5)	2078 (21)	1193 (22.4)	220 (22.3)	42 (18.2)
20% less on NIHSS	18786 (64.8)	10805 (65.7)	6490 (65.6)	3577 (67.2)	607 (61.4)	131 (56.7)

ECASS-2 indicates European Cooperative Acute Stroke Study 2; NIHSS, National Institutes of Health Stroke Scale; and SITS, Safe Implementation of Treatment in Stroke.

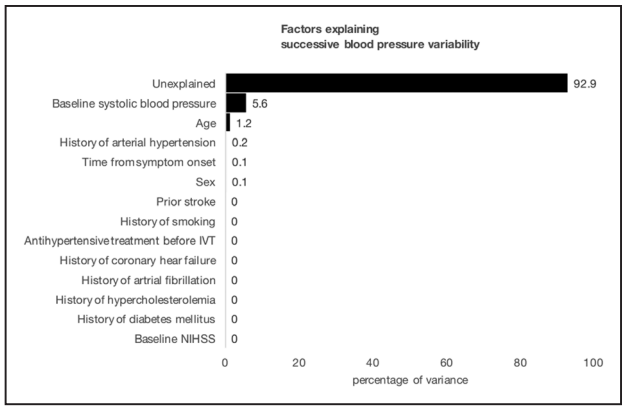

Figure 1. Baseline factors explaining successive blood pressure variability. IVT indicates intravenous thrombolysis; and NIHSS, National Institutes of Health Stroke Scale.

influential (5.55% explained variance), followed by age (1.18% explained variance). Interestingly, patients with history of hypertension were only marginally predictive for higher BPV_{SV} (0.2% explained variance). All other variables also explained <1% variance leaving 92% of the variance in BPV unexplained (Figure 1).

Outcome Analysis According to BPV_{SV}

Early Neurological Improvement

About short-term outcome, univariate analysis of BPV_{SV} was not significantly associated with $ENI_{20\%}$ (P=0.428) and ENI_8 (P=0.394). Adjustment with relevant confounders in multivariable analysis did not change this result (Table 2).

Three-Month Outcome

Excellent outcome was not significantly associated with BPV_{SV} by means of univariate (P=0.346) and multivariable (Table 2) adjustments.

Functional independency was less likely in patients with higher BPV_{SV} by means of univariate (P=0.021) and multivariable regression (Table 2) analyses.

A shift to the next higher (worse) mRS category (categorical shift) was more likely in patients with higher BPV_{SV} in multivariable regression analysis (Table 2).

Mortality within 90 days after stroke was more likely in patients who experienced higher BPV_{SV} (univariable, P=0.004; multivariable, Table 2).

Symptomatic Intracerebral Hemorrhage

In terms of safety, BPV_{SV} was associated with the presence of $SICH_{SITS}$ (P=0.0001) and $SICH_{ECASS}$ (P=0.0017). Adjustment in multivariable analysis reinforced these results irrespective of the bleeding definition used (Table 2).

Outcome Analysis According to Pre-Treatment BPV_{sys}

Higher BPV_{sys} was significantly associated with lower odds ratios for ENI, lower rates of favorable outcome at 3 months, and higher risk of SICH in multivariable analysis. No association with mortality was found (Table 2).

BPV_{SV} and Pre-Treatment BP_{sys} Interaction (BPV_{SV}-by-BP_{sys})

Determining outcome across the mRS at different levels of BPV_{SV} and across the range of BP_{sys} revealed an X-shaped relationship (Figure 2): BPV_{SV}-by-BP_{sys} interaction was found for outcomes of $ENI_{20\%}$ but not for ENI_8 for excellent and good functional outcome as well as for the shift analysis of the mRS. This relationship was not obvious for mortality and safety (Table 3).

Sensitivity Analysis of BPV_{SV}-by-BP_{sys} Interaction in Patients Presenting With No History of AF

Outcome analysis in non-AF patients on BP_{sys} and BPV_{SV} and their interaction was largely unchanged and is shown in Tables I and II in the online-only Data Supplement.

Discussion

In this study with a large cohort of ischemic stroke patients treated with IVT, we highlight the prognostic significance of successive BPV_{SV} for functional outcome after stroke and especially for safety. A novel finding in our study is the better prediction of short- and long-term functional outcomes when considering the reciprocal interaction of pre-treatment BP (BP_{sys} high, medium, or low) and the course of BP 24-hour post-thrombolysis (accounted by BPV_{SV}).

BPV in our study was associated with several definitions of functional outcome and safety. Importantly, these results were independent of BP_{sys} (a well-known predictor of safety[15,16] and functional outcome after stroke[4,6,8,13,34]). A post hoc analysis from IST-3 (The Third International Stroke Trial) reported an association of higher BPV with adverse events, the occurrence of SICH and poor 6-month outcome.[13] Our results may complement those in so far that we found short-term BPV to be of significance for safety (SICH) and several long-term outcome definitions. About short-term outcome (2-week outcome and in-hospital outcome), 2 most recent studies did not find any importance of BPV in outcome prediction.[22,23] Our results support these studies for the most part because we found no clear association of BPV with early neurological improvement too (ENI_{20} and ENI_8).

The overall comparability of those studies with ours is narrow because of smaller sample sizes, different acquisition of BP intervals, and various definitions of BPV and outcomes.

Pursuing the notion of both BP characteristics (BP_{sys} and BPV_{SV}) being relevant to several issues, we put both in context by analyzing whether patients with a particular pre-treatment BP would yield different functional outcomes with various degrees of BPV (Figure 2A and 2B). For patients who presented with normal BP_{sys}, neither high nor low BPV_{SV} seemed to influence the outcome in some way or other. However, patients presenting with low BP_{sys} seemed to benefit from low BPV_{SV}. Equally did patients with high pre-treatment BP_{sys} and high BPV_{SV}. This combination (high BP_{sys}+high BPV_{SV}) seems, for example, when physicians actively intervene on high BP_{sys} but may also be attributed to the natural BP course after stroke—the trend of BP to decline over time. In this regard, the post hoc analysis of IST-3 suggested similarly a good outcome at 6 months after stroke when BP lowering was more intense during the first 24 hours,[13] whereas other studies did not.[9–12,35] In patients in whom pre-treatment BP_{sys} is within the normal range, physicians usually restrain active elevation of BP (resulting in low BPV_{SV}). The combination of high BP_{sys} and low BPV_{SV} seems

Table 2. Adjusted Influence of Pre-Treatment Systolic Blood Pressure and Successive Blood Pressure Variability on Outcomes of Short-Term, Safety, and Long-Term Outcome

	Successive Blood Pressure Variability Odds Ratio (95% Confidence Interval)*	*P* Value	Pre-Treatment Systolic Blood Pressure Odds Ratio (95% Confidence Interval)†	*P* Value
Short-term outcome				
Early neurological improvement (NIHSS improvement 20%)	0.96 (0.93–1.00)	0.069	0.86 (0.82–0.90)	<0.0001
Early neurological improvement (NIHSS 8-point)	1.01 (0.96–1.06)	0.737	0.87 (0.82–0.92)	<0.0001
Outcome 90 d after stroke				
Excellent (mRS score of 0–1)	0.98 (0.94–1.02)	0.239	0.84 (0.80–0.89)	<0.0001
Functional independent (mRS score of 0–2)	0.94 (0.90–0.98)	0.002	0.89 (0.84–0.93)	<0.0001
Ordinal shift mRS (shift to next higher [worse] category)	1.04 (1.01–1.08)	0.014	1.14 (1.10–1.19)	0.014
Death (mRS score of 6)	1.10 (1.03–1.16)	0.002	1.06 (0.98–1.15)	0.135
Symptomatic intracerebral hemorrhage				
SITS definition	1.24 (1.10–1.40)	0.0003	1.24 (1.03–1.48)	0.02
ECASS-2 definition	1.14 (1.06–1.23)	0.0009	1.20 (1.08–1.34)	0.001

Adjusted for age, sex, baseline NIHSS, history of arterial hypertension, history of diabetes mellitus, history of hypercholesterolemia, history of smoking, history of atrial fibrillation, history of coronary heart failure, and prior stroke. ECASS-2 indicates European Cooperative Acute Stroke Study 2; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SITS, Safe Implementation of Treatment in Stroke.

*Indicating a 12-point change in blood pressure variability (=change from 25th percentile to 75th percentile).

†Indicating a 25-point change in systolic blood pressure (=change from 25th percentile to 75th percentile).

unfavorable, most probably because BP_{sys} remains too high because of lack of extrinsic or intrinsic modulation or because of insufficient response to possible interventions. An equally unfavorable combination seems to be low BP_{sys} and high BPV_{SV} that might be explainable by exceedingly BP lowering leading to cerebral hypoperfusion or vice versa unstable conditions and the need for interventional elevation of BP.

Overall, these results indirectly indicate that patients may benefit from BP management that is personalized. This hypothesis could (at least partially) explain inconsistencies in several observational studies on BP lowering, where some suggested much lower absolute BP_{sys} values to be favorable (range between 140 and 150 mmHg).[4,6,8] In contrast, several post hoc analyses of randomized clinical trials reported no advantage.[9–12,35] The BP arm of the ENCHANTED trial is still ongoing, possibly the results will offer insights about the importance of BP lowering in thrombolyzed patients.[17]

Certainly, BP management in the acute phase of stroke should include aspects of the presence of penumbra, presence of vessel occlusion, collateral flow, revascularization status,

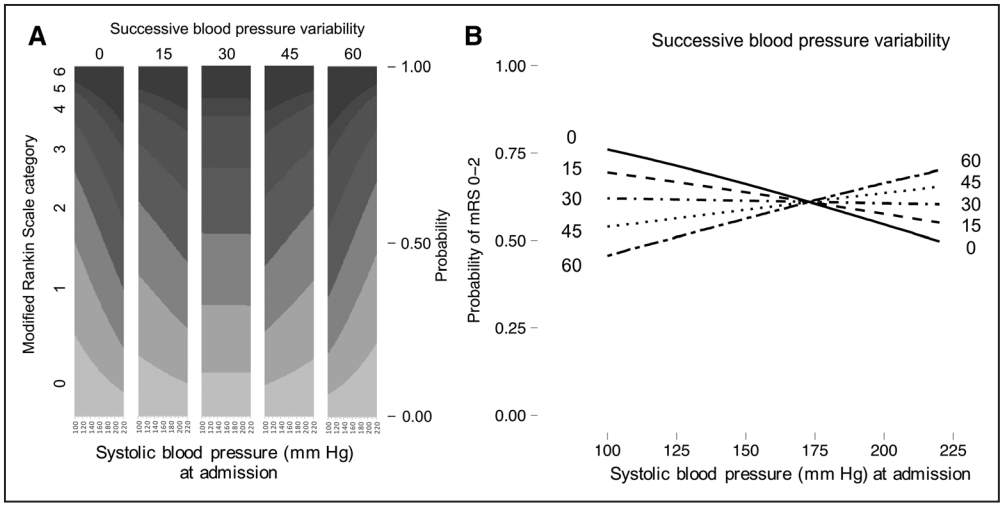

Figure 2. Relationship of pre-treatment systolic blood pressure (BP) and successive BP variability (BPV) influencing functional outcome. **A**, Probability of reaching modified Rankin Scale (mRS) category by range of pre-treatment systolic blood pressures; given are example categories of successive blood pressure variability (no=0, low=15, med=30, high=45, highest=60). **B**, Probability of good functional outcome (mRS score of 0–2) for conditioned values of successive BPV (0, 15, 30, 45, and 60).

Table 3. Relationship of Pre-Treatment Systolic Blood Pressure and Successive Blood Pressure Variability* Across Different Outcomes in All Patients

Interaction BP_{sys}-by-BPV_{SV} $P_{interaction}$	All (n=16 434)
Short-term outcome	
Early neurological improvement (NIHSS improvement 20%)	0.001
Early neurological improvement (NIHSS 8-point)	0.09
Outcome 90 d after stroke	
Excellent (mRS score of 0–1)	<0.0001
Functional independent (mRS score of 0–2)	0.002
Ordinal shift mRS (shift to next higher [worse] category)	<0.0001
Death (mRS score of 6)	0.11
Symptomatic intracerebral hemorrhage	
SITS definition	0.343
ECASS definition	0.352

BP indicates blood pressure; BPV, blood pressure variability; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SITS, Safe Implementation of Treatment in Stroke

*Multivariable regression analysis including multiplicative interaction of pre-treatment systolic BP and successive BPV adjusted for confounders of age, sex, baseline NIHSS, history of arterial hypertension, history of diabetes mellitus, history of hypercholesterolemia, history of smoking, history of atrial fibrillation, history of coronary heart failure, and prior stroke.

and stroke cause.[36] Although our analysis falls short to address these individual aspects because of its retrospective design, we interpret our findings a step toward a better understanding of BP and BPV in acute stroke.

The authors may also point toward a better understanding of variability as BP characteristic (see Manning Stroke 2015 for review[18]). In observational studies, where BP management is not actively monitored, it is unclear what we exactly measure when we measure BPV. BPV is under the influence of numerous extrinsic (administered and preexisting medication, arrhythmia requiring β-blocker, vegetative and emotional stressors, and positional [eg, lying versus upright] and continuous recording versus manual measurement) and intrinsic (arterial hypertension, fluid balance, stroke subtype, recanalization, and autonomic regulation or dysregulation) factors.[37,38] Even so, attempts to explain BPV in the multivariable analysis by all available patients baseline characteristics left 92% variance unexplained in our study.

Interestingly, BP_{sys} was the strongest predictor for BPV. As for some definitions of BPV, this could easily be explainable because pre-treatment BP_{sys} influences, for example, SD to a certain extent (depending on the number of available BP readings). Therefore, we considered a similar type of influence for the variability measure chosen in this study (successive BP variability). In the SITS International Thrombolysis registry, BP is documented at only 3 time points. This is because to minimize the workload of the investigator because the SITS IVT protocol has ≈200 other variables. The individual centers were not required to standardize their protocol when measuring BP—both facts that might lead to bias in interpretation of BP and BPV. In routine clinical practice, BP is measured at least hourly after IVT up until follow-up imaging, but unfortunately these additional data are not available in the SITS registry. However, as shown in the online-only Data Supplement, we demonstrate that the variability formula of BPV_{SV} is less prone to single values.[25] This also improves plausibility that our finding of BP_{sys}-by-BPV_{SV} interaction is not explainable as a by-product of the chosen BPV definition.

Besides the main limitation of uncontrolled data and retrospective analysis, our study has additional limitations. Although we demonstrated no influence of NIHSS or other baseline factors on BPV in linear regression, BPV may still be an epiphenomenon of clinical parameters, for example, severity of stroke, lesion growth (as demonstrated by Delgado-Mederos et al[39]), or BP lowering interventions. We present an effect of the interaction between BP and BPV for the whole cohort and for those patients without AF, but most likely, there were subgroups of patients (different stroke causes, presence of penumbra, vessel occlusion, recanalization status, and collateral flow) for whom this interaction might be more or less relevant. None of these factors was investigated in a well-structured way with respect to BPV.

Because of the retrospective design of this study, we were not able to control neither for a single nor much less for all of those variables. Only about a half of all patients registered in SITS were further analyzed, and after preprocessing, only 16 434 patients (28%) remained; this is an important limitation of the study. Matching may reduce overall degree of bias; however, it has to be stressed that control of unobserved variables—as in randomized trials—is not possible.

Despite these limitations, we interpret our findings as novel and significant with implications for patient care and future studies. The main strength of our study is that it comprises by far the largest cohort of IVT-treated patients in whom this analysis has been completed.

Conclusions

BP variability during 24 hours after thrombolysis is of significant but currently under investigated relevance for stroke outcome. Putting the course of BP 24 hours post-thrombolysis in relation to its pre-treatment value significantly improved the prediction of specific short- and long-term outcomes of stroke in this study. Thus, future clinical trials should carefully consider both—pre-treatment BP and its variability over time.

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Disclosures

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